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Pharmaceutical Approach of Nano- Particles as a Targeted Nasal-Brain Delivery System

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Abstract

The first study reported for nasal brain drug delivery was in 1937.The uptake of nasal - brain drug delivery, has received a great deal of attention as a convenient, method for the systemic administration of drugs. Which are low less effective orally and, only effective if administered by injection, many well-known different pathways and routes for drug absorption via the nose are affected by various factors. Some of them are factors related to the natural physiology of the nose and mucociliary clearance, enzyme, blood flow in the nasal cavity, and diseases. The bio-fate of drugs instilled in nasal cavity, is mainly affected by the pharmaceutical and pharmacokinetic properties of the drugs Pharmaceutical nanoparticulate carriers, also known as nanomedicines, offer numerous benefits for delivering neurotherapeutics from the nose to the brain. Most types of nanocarriers have been extensively researched for this purpose, including nanoemulsions and solid-lipid nanoparticles (SLNs), and nanosuspensions.However, there are multiple potential problems associated with the intranasal route of administration of nano carriers, such as, toxicity and irritation of the nasal mucosa, stability of nano-carriers inside the nasal membranes, and possible degradation of enzymes during passage. In general, the adherence of the traditional formulation to the mucosal membrane of the nasal cavity can be enhanced by including synthetic polymers such as Eudragits®, which are derived from acrylic and methacrylic acid. The destiny of nanocarriers is determined by their inherent physicochemical characteristics. For example, the characteristics that can be considered include the composition, particle size, surface charge, as well as surface hydrophobicity or hydrophilicity. Different experimental models were used in the published studies, like *in vitro*, *in vivo* and *ex-vivo* models, besides to cell culture and, cell line models. This quantitative analysis must be revealed as blood- brain drug ratio, besides to absolute, and relative bioavailability of the drug delivered by the brain Moreover, qualitative analysis should be recognized for most of nano particle's morphology like optical imaging, brain histopathology, fluorescence microscope, and gamma scintagraph. In the following review article, aims are provided a detailed review of literature concerning direct nose-to-brain drug delivery.

Keywords: Delivery-System, Intranasal, Pharmacokinetic, Nanoparticle, Nose-To-Brain Targeting

Introduction

Anatomy of nasal cavity

The external nose, nasal cavity, paranasal sinuses, and nasopharynx make up the human nose. The nasal septum longitudinally separates the nostrils and nasopharynx. The human nasal cavity has a length of around 12-15cm and an absorptive surface area of 160cm2. This is owing to the presence of three bony structures known as inferior, middle, and superior , which play a role in filtering, humidifying, and warming the air that is breathed in [(1)]. The nasal cavity has four forms of epithelia: squamous, respiratory, transitional, and olfactory [(2).] The respiratory and olfactory epithelia are particularly important since they are the primary locations where drugs are absorbed following intranasal delivery. The features of the human nasal epithelium are compared to those of various species and are reported in Table 1.

Table1.Nasal cavity characteristics of human and various animal species [(3)]

Species	Surface area (cm^2)	Volume(cm^3)	Length (cm)	Olfactory region (cm^2)
Human (70 kg)	181.0	19.0	8.0	20.0
Sheep (40 kg)	327.0	114.0	18.0	14.4
Rabbit (3 kg)	61.0	6.0	5.2	9.3

Humans' external noses enclose the nostrils and a third of the nasal cavity, which has two five- and ten-centimeter chambers. Muscles cover bony-cartilaginous roof. Nasal cavities protect the nasal mucosa, but its main use is ornamentation. Upper lateral cartilages and fibrous tissue surround the

anterior nasal cavities and regulate airflow. Regenerating alar cartilages can withstand inspiration pressure. [4]. The septum splits the nasal cavity longitudinally into left and right parts. Septum is posterior bone and anterior cartilage. [5].It moves through a 12–15 cm, 20 mL.150–160 cm2 anteroposterior channel from the nostrils to the nasopharynx. Before entering the lungs, the nasal cavity purifies, olfactory perceives, filters, heats, and humidifies air. [6]. about 10% of the nasal cavity is olfactory. This structure is partially on the nasal septum and partially on the superior turbinate, 7 cm from the nostril in the upper nasal cavity, beneath the cribriform plate of the ethmoid bone. [7].This structure's specialized olfactory receptors detect smells. Epithelium with pseudostratified columnar structure makes up these receptors. The neuroepithelium is the only central nervous system component that interacts with the environment. [8].A nerve fiber on each side travels through the cribriform plate of the ethmoid bone to the olfactory bulb.

Nasal physiology

On average, a person inhales approximately 10-20 breaths per minute, resulting in the intake of around 10,000 liters of air every day, which varies in terms of temperature and humidity. The nose serves multiple tasks, including sensing, immunological function, olfaction, filtration, air conditioning, and protection, all of which contribute to preserving aerodynamics and facilitating speech. [9].

Sensation

Nasal feeling comes from nerve terminals in the nose lining. They cause discomfort or burning when provoked by certain chemicals. Pain and burning can trigger defense reflexes including sneezing, tears, and nasal secretions. [10].

Immunology

Nasal secretions contain IgA, IgG, IgM, and IgE. Local immunity and allergies are also supported by lysozymes, lactoferrin, and nasal mucosal neutrophils and lymphocytes. ACPs and lymphocytes also contribute. [9, 10]

Olfaction

Olfaction refers to the perception of smell that occurs when odorous substances are detected, in addition to hearing, taste, vision, and balance. The human olfactory system is capable of perceiving odors by means of the numerous olfactory sensory neurons located on the olfactory epithelium. The human nose can detect approximately 10,000 distinct odors. It happens when a scent attaches to receptors of odorant-binding proteins in the nasal cavity, conveying the signal to the olfactory system and ultimately to the brain. In addition, olfaction serves other purposes such as identifying potential dangers and recognizing pheromones, while also contributing to the sense of taste [10, 11].

Filtration

The thick cluster of hairs within the nostrils facilitates the filtration of inhaled air, preventing the entry of dirt and dust particles into the lungs. Particles with a size greater than 30mm are eliminated because the nasal airway experiences significant air turbulence, resulting in prolonged contact between the air and the mucosa. Although a significant percentage of tiny particles measuring 10mm are also removed through filtration. [9].

Air conditioning

The nostrils of the nose play a crucial role in safeguarding the airways from unconditioned air. During periods of rest and light physical activity, a significant number of persons inhale and exhale exclusively through their nasal passages. Nevertheless, with heightened physical activity, the nasal passages were able to intake a significant amount of air. Subsequently, the air with the lowest level of conditioning is ejected from the trachea bronchial tree and flows across the mucosa of the pharynx [12].According to estimates, a typical, physically fit adult living in a moderate climate would lose between 300 to 400 milliliters of water. Despite receiving a significant volume of inspired air, the nose is able to humidify the air to a level exceeding 80% before it reaches the lungs. The air is heated by the mechanisms of conduction, convection, and radiation, facilitated by blood circulation. [13].

Protection

The mucous layer serves as an additional protective mechanism of the nose. The object is composed of two distinct layers. The outer layer exhibits a reasonably high viscosity and is situated over a thin layer of serous fluid. The usual resting nose secretes approximately 20-40mL of mucus per day from a surface area of 160cm2 of the nasal mucosa. The mucus flow in the human nasal fossa primarily moves towards the nasopharynx in a posterior direction. The velocity of mucociliary transport is 1–2mm/h posterior to the front section of the inferior turbinate. When there is a defect in the mucosal surface, the mucus maintains its cohesive characteristics, allowing it to travel smoothly from one intact epithelial edge to another. If squamous metaplasia is present, it will result in the loss of normal mucociliary transport at this location. [13].

Drug transport pathways from the nose to the brain

Medicines go from the nasal epithelium to the brain via clear and unclear pathways. Nose-to-brain drugs must cross the nasal epithelial barrier via intracellular or extracellular routes to reach the CNS. [14]. Intraneuronal translocation to the olfactory bulb or transcytosisfollows endocytosis into olfactory sensory neurons (OSN) in the olfactory epithelium. Nasal trigeminal nerves can transport

viruses and bacteria to the CNS. [15].The lamina propria is reached by paracellular diffusion through olfactory system extracellular transport channels. The nasal olfactory and respiratory epithelia may become empty due to cell turnover throughout life. This could allow larger molecules to access the lamina propria through cell gaps. The nasal epithelial barrier may distribute drugs differently in the olfactory and respiratory domains. To find the best technique to transport drugs or other biogenic chemicals to the brain, focus on one of these locations. Thus, future study should examine how formulation can improve nose-to-brain drug transport. [16].

The pharmacokinetics of intranasal to brain therapeutics

Absorption

The first and initial stage in achieving pharmacological effects of intranasal brain therapies is the absorption process, which relies on the permeability of the mucus barrier. Various factors influence the methods and pathways of medication absorption through the nasal route. Numerous studies have documented the multitude of factors that exert an influence on the absorption of medications delivered via the nasal route. The physiology of the nose and mucociliary clearance (MCC) is influenced by a number of factors, including nasal cavity blood flow, enzymes, and various diseases. A range of properties, including molecular weight, size, chemical structure, lipophilicity, solubility, partition coefficient, and pKa, are classified as drug-related factors. Conversely, formulation-related factors encompass characteristics such as particle size, osmolarity, viscosity, drug concentration, dose volume, administration frequency, and excipient properties inherent in the formulation. [17].Various methods for improving bioavailability, including as absorption enhancers and formulation modifiers, have been documented for enhancing in vivo absorption [18].The utilization of chitosan polymer as a mucoadhesive agent is attributed to the existence of cationic amine group. The glycyrrhizic acid nanoparticles that were synthesized had an average particle size ranging from 100 to 300 nanometers. The Wister rat was utilized to determine the in vivo absorption of glycyrrhizic acid. The results indicated that the NPs' hydrophobic surface led to increased absorption and a longer duration of time in the nasal cavity. [19].

Distribution

Distribution refers to the additional step involved in the transportation of biopharmaceuticals and therapies from the point of administration to the target site. The distribution of nasal brain therapies in the brain may vary due to differences in tissue affinity. The experimental results demonstrated the impact of several conditions on the distribution of medications in the brain in living organisms. The primary determinants influencing the distribution of a medicine within a living organism include its capacity to pass through biological barriers, the size of its molecules, its acidity or basicity, the size of the tissues it targets, its affinity for attaching to other substances, and characteristics specific to the patient.

In their study, Wang et al. (2020) investigated the in vivo distribution of rotigotine (ROT) using a thermo-sensitive hydrogel in Sprague-Dawley rats. They prepared ROT solution, ROT-loaded polymeric micelles (ROT-PM), and ROT-loaded polymer micelles thermo-sensitive gel (ROT-PM-TSG), which were administered intra nasally to determine their distribution in brain tissue. The acquired results have verified that the intranasal delivery of ROT is a viable choice for specifically targeting the brain. [20].

Metabolism

Drug metabolism is the process of detoxifying drugs. Intranasal injection of nasal brain medications is used to circumvent first-pass metabolism through the liver or gastrointestinal tract (GIT). The production of bio metabolites after intranasal delivery was observed. This could be due to the deliberate avoidance of the initial breakdown of a substance in the body, known as first-pass metabolism, or the presence of small amounts of byproducts that are produced in the brains of both humans and animals. Furthermore, the metabolic activity of the nasal cavity is reduced in comparison with that of the liver and gastrointestinal tract (GIT). Research has been conducted to evaluate the in vivo metabolism of Loxapine when delivered via intranasal, oral, and intramuscular routes. Loxapine, when taken by mouth, is converted into 7-hydroxy loxapine by metabolism. A comparison was made between the metabolic event of loxapine after oral and intranasal delivery, and the amount of drug detected in various brain areas. The metabolism was observed to be 10 times lower with intranasal delivery compared to oral administration. [21].

Elimination

The medication is typically eliminated through the processes of metabolism and excretion. Elimination happens through two primary mechanisms: renal excretion, which involves the kidneys, and nonrenal excretion, which involves the lungs, liver, colon, sweat glands, and salivary glands. The medication therapies delivered intranasally for brain targeting are primarily removed via renal clearance [22].Hammarlund et al. (2008) conducted a study on the removal of drugs from the brain, specifically looking at the passive elimination of drugs from the brain tissue. A mathematical modeling approach was used to investigate the removal of remoxipride from the brain following intranasal delivery. The clearance rate following intranasal administration was more sluggish in comparison with intravenous injection.

The decreased elimination rate following intranasal delivery suggests that the rate of absorption at the intranasal location affects the elimination process, known as flip-flop kinetics. [23].

Brain targeted drug delivery system through the nose

The medications can be delivered into the brain tissue either directly through the olfactory bulb or by the cerebrospinal fluid (CSF) from the nasal cavity. Drugs can also be conveyed to the brain through trigeminal nerve receptors located in the nasal cavity.[24].Alternatively, it is possible that the transportation of the substance occurs within the cell, potentially entering the neurons by endocytosis or pinocytosis pathways[25].In 1937, the initial investigation documented the potential for a direct pathway from the nasal cavity to the brain, following the introduction of a dye into the nostrils of rabbits.[26].The primary objective of a targeted delivery system is to keep the necessary drug concentration in the plasma and tissues at specific places, hence minimizing any harm caused to normal tissues by the drug. Targeted drug delivery involves the active transportation of drugs to specified tissue compartments with high activity, while minimizing drug concentration in normal cells. The primary objective of a targeted drug delivery system (TDDS) is to achieve localization and preservation of therapeutic properties, as well as to ensure a specific route for drug administration, minimize medication adverse effects, and extend drug contact with the affected tissue. A targeted delivery system must effectively maintain the desired drug concentration in both plasma and tissues at the intended target site [27].The criteria of smart TDDS must fulfill the following [28]:

(1) Resistant to degradation by any bodily fluids,

(2) Enhance the drug's concentration when administering it to the specific area of the body.

(3)Enhance the effectiveness of pharmacological treatment to minimize adverse reactions,

(4)The substance that is administered must be able to pass through a biological membrane in order to be absorbed.

(5) The medicine must be released in precise dosages to the specific targeted bodily area.Meanwhile the efficient TDDS ideally should possess the following properties [29]:

(1) Non-toxic, biocompatible, and chemically stable, both inside the body and in laboratory conditions,

(2) Limit the dispersion of drugs to cells, tissues, or organs that are not the intended target.

(3) Applicable and foreseeable medication release rate,

(4) Minimal medication seepage during transportation.

(5) The preparation should be straightforward, easily reproducible, and cost-effective.Conversely, an optimal drug carrier must exhibit the following characteristics to effectively transport drugs to specific targets. [30]:

(1) It must have the capability to traverse the anatomical barrier.

(2) The target cell should clearly and precisely recognize it in a selective manner.

(3) The drug-legend bong must exhibit stability in bodily fluids, followed by the carrier's release of the drug within the specific target tissue or organ.

(4) The substance must possess the qualities of being non-toxic, non-immunogenic, and biodegradable.

Biopharmaceutical considerations for nose-to-brain drug delivery

One of the main hurdles in drug delivery to the brain is the presence of BBB that affects the diffusion of drugs from the systemic circulation into the CNS even, if it is disrupted in certain disease conditions. Nowadays, more recent advancements were made in this field of the systemic drug deliver; the nasal route has created a great interest for the delivery mainly for small molecules and vaccines, giving alternative to the parenteral and oral systemic delivery [31].Intranasal administration offers, a practical, safe, and convenient alternative to various conventional drug delivery techniques as a transport pathway for the direct delivery of drugs effectively to the CNS, bypassing the BBB [32].The permeable nasal barrier is richer in vascular zed sub mucosa, and avoidance of the first-pass hepatic metabolism. The key provided by the intranasal drug administration, bringing a quick action, and improved brain bioavailability, and high patient acceptance [33].The bio fate of drugs instilled in nasal cavity is mainly affected by the pharmaceutical and pharmacokinetic properties of the drugs, and these properties are summarized as various factors affecting the absorption and permeability of drugs for the efficient nose-to-brain drug delivery, as shown in Table 2

A- Physicochemical considerations [34, 35, 36].

1. Characteristics of drugs
2. Formulations of drug formulations

B- Biopharmaceutical considerations [37, 38, 39].

1. Biological factors
2. Physiological factors

C- Practical considerations [40, 41, 42].

1. Nasal drops
2. Nasal sprays

Table2. Factors affecting drugs nose to brain delivery

Physicochemical properties	Formulation properties	Biological Physiological properties	Practical properties
1-Molecular wt. and Molecular size	1-pH	1-Nasal blood flow	1-Head position Drug administration
2- Chemical form	2 -Osmolarity	2-Area of membrane	2-Volume of dose
3- partitioncoefficient. (K)	3-Viscosity	3- Nasal secretion	3-Frequency of dose
4-Dissociation constant (Ka)	4-Physical formulation	4-Mucociliary clearance	4-Angle of spray
5-Lipophilicity	5-Dosage form	5-Site of deposition	5-Inhalation
6- Solubility	6-Exciepient	6-Pathological condition	6-Type of delivery device
7-Polymorphisim		7-Enviromental conditions	
8- Morphology			

Nanocarriers for nose-to-brain drug delivery

The substantial nanomedicine market provides clear proof of the immense potential of applying nanotechnology in the medical field to enhance the treatment of numerous ailments. The US Food & Drug Administration (FDA) has granted approval to multiple nanomedicines. Nano medicines are currently leading the way in the development of new drug delivery systems. A surface modification strategy has been introduced to enhance the targeting ability of nanomedicines. This approach aims to selectively target drugs, and it was inspired by Paul Ehrlich's magic bullet concept. [43]. Pharmaceutical nanoparticles, also known as nanomedicines, have numerous benefits when it comes to formulating and delivering neurotherapeutics to the brain through the nose. Most of the research conducted thus far has focused on using different types of nanocarriers, such as nanoemulsions and solid-lipid nanoparticles (SLNs), for this purpose.[44]. nanostructured lipid carriers (NLCs), liposomes [45]. polymeric nanoparticles [46]. albumin nanoparticles, gelatin nanoparticles [46] dendrimers[47]

Properties of nanocarriers for nose-to-brain drug delivery

The fate of nanocarriers is dictated by their intrinsic physicochemical properties. The characteristics of nanocarriers, such as their composition, size, surface charge, and surface hydrophobicity or hydrophilicity, might influence how they interact with the biological environment, specifically:

a.Nanocarriers engage with the mucus layer and deliver the medicine either within the mucus or at the boundary between mucus and epithelial cells.

b. Medication-loaded nanocarriers have the ability to traverse the mucosal barrier and migrate along nerve axons to reach the brain, where the medication is subsequently released.

c.Drug-loaded nanocarriers can be absorbed by the respiratory epithelium and/or the olfactory neuroepithelium, where the drug is subsequently released. The released drug then spreads across the perineurial space and enters the central nervous system.

A study conducted in 2017 [48]. Demonstrated that nanoemulsions, with droplet sizes ranging from 80 to 900nm, remained in the rat nasal cavity for a duration of 0.5 to 16 hours following the application of 100mL of the formulation. It was noted that there is a direct correlation between droplet size and retention time in the nasal cavity, with smaller droplets having longer retention times. Another study (Kanazawa et al.) also discussed the correlation between the distribution of the brain and the properties of nanocarriers [49], in (2011) by using peptide-based carriers. The development of safe, effective, and stable nanomedicines remains an important criterion in the perspective of targeted therapeutics [50]. Currently, the most appealing feature of nanotechnology-based medication delivery is the advancement of surface-modified nanocarriers that exhibit a strong affinity for certain receptors.

Nanomedicines and ligands for surface modification of nanocarriers

The primary studies on surface-modifying macromolecules for targeted nanomedicine development have examined numerous agents utilized to generate surface-modified nanocarriers. Designed for the targeted administration of drugs directly to the brain via the nasal route, these are:

1. Lectins as surface-modifying ligands
2. Lactoferrins as surface-modifying legends
3. Cell-penetrating peptides (CPPs) as surface-modifying legends

Delivering nanocarriers through the nasal route to the brain has the potential to be a highly adaptable method for addressing the difficulties associated with neurotherapeutics. Various drug delivery technologies, such as polymeric nanoparticles, polymeric micelles, polymer-lipid hybrid nanoparticles, and lipid-based nanocarriers,

have been investigated for the purpose of delivering drugs through the nose-to-brain pathway. Nevertheless, the intranasal administration of nanocarriers presents other potential obstacles, including the risk of toxicity and irritation in the nasal mucosa, the stability of nanocarriers in nasal membranes, and the potential for enzymatic breakdown during passage. The adherence of the classic formulation on the mucosal membrane can be enhanced by using synthetic polymers such as acrylic and methacrylic derivatives, as well as natural biopolymers like chitosan or cellulose derivatives. [51].

Medicinal and pharmaceutical applications of direct nose-to-brain delivery

Consequently, the nasal cavity plays a critical function in safeguarding against airborne illnesses. It functions efficiently by humidifying and filtering inhaled air prior to its entry into the respiratory system; the hair lining captures any inhaled particles or microorganisms.

At present, the nasal route is being utilized extensively to administer medications for the treatment of nasal allergies, sinusitis, nasal infections, and nasal obstruction, among other local ailments. [52].While intra-nasal drug delivery does offer a number of benefits; its primary drawbacks are high clearance, restricted accessibility due to enzymatic degradation, and anatomical constraints imposed by the nasal cavity. In order to enhance the pharmacological effects on the primary peripheral organs, prevent enzymatic degradation, and prolong the residence time of the drugs within the nasal cavity, an ideal formulation would be necessary. To accomplish these objectives, the following formulation criteria have been utilized :[53]

1. Nasal enzyme inhibitors
2. Permeation enhancers
3. Pro drug approach
4. Structural modification

Moreover, many applications are used in fields of direct nose-to-brain delivery systems are:

- Delivery of macromolecules
- Delivery of genes
- Vaccine delivery
- Tissue engineering
- Diagnostic applications

Some of the marketed and investigational nose-to-brain targeted products are listed in Table 3.

Table3. Nasal products for brain drug delivery on the market and under in clinical trials[54, 55]

Brain disorder	Brand/ candidate Drug	Drug	Dosage form
Migraine	AscoTop/ Zomig	Zolmitriptan	Solution (Spray)
Pain	Rylomine	Morphine	Solution (Spray)
Smoking	Nicotrol NS	Nicotine	Solution (Spray)
Cessation	Syntocinon	Oxytocin	Solution (Spray)
Cranial diabetes	DDAVP	Desmopressin	Solution (Spray)
Insipid us	Nasal inhaler	Clonazepam	Phase II, completed
Epilepsy	Nasal inhaler	Midazolam	Phase II

Evaluation of direct nose-to-brain drug delivery

The transportation of medications into the cerebrospinal fluid (CSF) and brain tissues necessitates the investigation of models specifically designed for direct drug delivery from the nose to the brain. Experimental modeling is used to specifically target and obtain a desired therapeutic response, which is essential in the drug discovery and development procedures.

Experimental models

In vitro models, such as primary cell cultures of human nasal epithelium (HNE), offer insights into drug penetration, metabolism, and toxicity. However, it does not encompass the variances that arise from the diversity across different species. [56].Initial absorption investigations were primarily conducted on mouse and rat models, while rabbit, dog, and sheep models were preferred for pharmacokinetic calculations. Pharmacokinetic and bio distribution studies are essential for determining the speed and scope of medication distribution once it is administered. [57].Hence, before employing any of the previously stated models, it is necessary to conduct computational assessment as a means of screening and selecting the most suitable models. [58].

1. In vitro models

Nasal cell specimens can be obtained from the vestibular region, atrium, or turbinate, which are the anticipated sites of formulation deposition. The segment, located in the middle and inferior turbinate, consists of basal cells and is lined with a pseudo stratified columnar epithelium. Previous research has examined the impact of protease inhibitors on the absorption enhancement of methionine enkephalin using human nasal tissues obtained during elective surgery. The nasal epithelium was treated with pronase, then filtered and preplated in an environment with minimal fibroblast contamination, composed of 95% O2 and 5% CO2. The brushing technique is employed to

gather cells without the need for anesthesia. [59]In addition, various models, such as the reconstructed human nasal mucosa model, was utilized to advance the research on medication delivery to the brain through the nasal cavity. [60]cell culture model [61]cell line model [62]. [63].

2. Ex vivo models

The nasal mucosa specimens were collected from many animal species including rabbits, sheep, cows, and pigs. This method is valuable for conducting ex vivo screening of intranasal drug transport to investigate penetration, metabolism, efflux, and toxicity. The isolated excised tissue model [64].as an ex vivo nasal perfusion model—Using chamber model[65]The following table 4, demonstrate some important investigations of various models useful in direct nose-to-brain drug delivery.

Table4. *In vivo* models investigated for some direct nose-to-brain drug delivery.

Therapeutic drug	Disease	In vivo animal model	References
Rotigotine	Parkinson's disease	Male Kunming mice (4–5weeks old)	[66].
Bromocriptine	Parkinson's disease	Adult Swiss albino mice (20–40g)	[67].
Tarenflurbil	Alzheimer's disease	Sprague–Dawley rats	[68].
Donepezil	Alzheimer's disease	Adult male Wistar rats (180–220g)	[69].

3. In vivo models

The pharmacological effects are governed by the accessible free drug concentration at the target site, which is one of the acknowledged requirements. The medications are formulated using a carrier molecule that controls the concentration of active pharmacological components at the desired location. [70]During experiments, a challenge arises when cerebrospinal fluid (CSF) samples become contaminated with blood, particularly when smaller animals are chosen for the investigation. The passage of a drug from the nose to the brain via a dose form must undergo thorough in vivo testing. Hence, a thorough understanding of the anatomical structure of the nasal cavity is crucial prior to choosing an appropriate animal model. The use of rodent models is broadly recognized in this study. [71], it is widely acknowledged that the pharmacological effects are produced by the free drug concentration at the target site. Incomplete drug release is the primary factor that affects the concentration of free drugs. This might lead to the undesired accumulation of drugs in compartments other than the ones intended for sampling, such as blood or tissue. Gaillard et al. observed that there is an increased possibility of CSF samples being contaminated with blood, particularly when a small number of experimental animals are utilized in the investigation. [72]The rats were positioned in a slanted position, with their backs restrained, to accurately assess medication targeting through nose-to-brain drug administration. [73]The formulations were introduced into each nostril using a Hamilton syringe equipped with a polyethylene tube (0.1mm ID) at the delivery site. The formulations were supplied at the entrances of the nostrils, with a volume of 10-12 mL per nostril. [74]Lu et al. [75]Quantified the apomorphine hydrochloride concentration in cerebrospinal fluid (CSF) by administering it intranasal and compared it with the drug concentration in plasma following intravenous and subcutaneous (SC) treatment in rats.[76]There is different models used to study the pharmacokinetic parameters of nasal brain delivery system, summarized as follows:

- Nonhuman primate models [77].
- Nonmammalian models [78].
- Genetic models [79].
- Viral vector models [80].

Estimation of dosage regimen for nasal brain delivery system

Transnasal delivery of neurotherapeutic substances such small medications, macromolecules, enzymes, hormones, viral vectors, and stem cells to the brain is becoming increasingly reliable. This method has shown promise in animal and human studies. The intranasal (IN) route terminates at the olfactory neuroepithelium or respiratory epithelium in the nose cavity via the olfactory and trigeminal nerve networks of the brain. After intranasal drug administration, brain drug estimation may be qualitative or quantitative.

Quantitative analysis

Drug Targeting Efficiency (DTE) is an important measure of brain drug exposure after intranasal (IN) versus intravenous (IV) treatment. The area under the curve (AUC) of drug concentrations against time profiles in the brain or blood after intranasal (IN) or intravenous (IV) administration can estimate drug transport efficiency (DTE). Use the formula below. [81]:

$$\mathrm{DTE}\ (\%) = \frac{[(\mathrm{AUC})\ \mathrm{brain} \backslash\ (\mathrm{AUC})\ \mathrm{blood}]\ \mathrm{IN}}{[(\mathrm{AUC})\ \mathrm{brain} \backslash (\mathrm{AUC})\ \mathrm{blood}]\ \mathrm{IV}} * 100$$

Brain-blood ratio

Typically, neurotherapeutics with a brain-blood ratio between 0.3 and 0.5 can effectively pass across the blood-brain barrier (BBB). However, those with a ratio larger than 1 can readily traverse the BBB. The primary options for improving brain targeting by increasing the brain-blood ratio are utilizing nanocarriers, mucoadhesive polymers, and modifying the surface of drug delivery carriers., [82]Authors suggest utilizing specific terminologies and/or criteria to show the brain-targeting efficacy of neurotherapeutics.

Pharmacokinetic study requires the use of both in vitro and in vivo experimental models to assess the efficiency of drug delivery devices targeting the nose-to-brain pathway. [83]. The computation of absolute brain bioavailability must take into account the brain's AUC0-t values, rather than those of the blood, when comparing drug accumulation through intranasal (IN) administration vs intravenous (IV) administration. The mathematical expression formula is used to assess this bioavailability:

$$(\text{B brain}) \text{ abs.} = \frac{[(\text{AUC}) \text{ brain}] \text{ IN}}{[(\text{AUC}) \text{ brain}] \text{ IV}} * 100$$

The relative brain bioavailability is a metric that quantifies the accumulation of a medication in the brain when administered through the intranasal route using a drug-loaded nano carrier system, as compared to an intranasal drug solution. The mathematical procedure used to calculate the relative brain bioavailability is:

$$(\text{B brain}) \text{ rel.} = \frac{[(\text{AUC})\text{brain}]\text{IN} - \text{nanocarrir}}{[(\text{AUC}) \text{ brain}] \text{ IV} - \text{solution}} * 100$$

The total quantity of drug that passed through the nasal mucosa per unit surface area was graphed against time, and the inclination of the linear portion of the graph was denoted as the steady-state flow of the drug. The apparent permeability coefficient (Papp) and steady-state diffusion coefficient (D) were determined by applying the following formulae.

$$\text{Jss} = \Delta\text{Qt}\,\Delta\text{ts}$$

$$\text{Papp\%} = \text{Jss} \setminus \text{Co x100}$$

$$\text{D} = \text{Papp x L}\setminus\text{K}$$

Where:ΔQt represents the total amount of medication that has passed through a certain area of the mucosal surface, measured in milligrams per square centimeter (mg.cm _2). The variable t represents the duration of time in hours. Co refers to the initial concentration of the drug in the donor compartment, measured in milligrams (mg). S represents the surface area of nasal mucosa that is either exposed or effective. K represents the partition coefficient of the drug-D nanoparticle, whereas L is the length of the diffusion path.

Qualitative analysis [85].

This type of drug delivery estimation, and evaluation may include different tests, these are: Optical imaging [86].Brain histopathology. [87], Fluorescence microscope [88].Gamma scintigraphy [89], Magnetic resonance imaging (MRI) [90].Positron emission tomography (PET) [91].

Conclusion

The human nasal cavity serves as a crucial route for drug administration, with inhalation of approximately 10,000 liters of air each day, which may vary in temperature and humidity. Various factors influence pathways of nasal medication absorption. Multiple studies have documented numerous factors that influence the absorption of drugs administered through the nasal route. Several factors influencing nasal physiology and mucociliary clearance. like enzyme activity, blood flow, and disease [92].Nanomedicines, and carriers made of various polymers, have numerous benefits when used in the formulation for delivering drugs from the nose to the brain. All types of nanocarriers, such as nanoemulsions, solid-lipid nanoparticles (SLNs), and nanosuspensions, have been examined for their potential in delivering drugs from the nose to the brain. These polymers are used to deliver treatments through the nose-to-brain route. Despite advancements in pharmaceutical drug product development, the intranasal administration of drugs embedded with nanocarriers presents several potential challenges. Among them toxicity and irritation, stability of nanocarriers, and possible enzymatic degradation during passage [93].The use of the standard formulation on the mucosal membrane of the nose cavity can be improved by using synthetic polymers such as acrylic and methacrylic acid derivatives (Eudragits) and natural biopolymers like chitosan or cellulose derivatives. The ultimate destiny of nanocarriers is determined by their inherent physicochemical characteristics. Which include the composition, dimensions, electric charge on the surface, as well as the surface's ability to repel or attract water [94].Despite the numerous benefits of intra nasal medication delivery, limited bioavailability caused by enzymatic degradation, rapid clearance, and anatomical limitations of the nasal canal pose significant challenges to this method of delivery. Furthermore, it is important to acknowledge the significance of qualitative analysis in assessing the morphology of nanoparticles, such as optical imaging, brain histology, fluorescence microscopy, and gamma scintigraphy. The dose regimen for a nasal brain delivery system requires a quantitative study to estimate the drug efficiency (DTE). This analysis is critical in determining the effectiveness of the drugs following intranasal (IN) administration compared to intravenous (IV) one.

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Conflicts of Interest

There was no conflict of interest regarding the publication of this manuscript.

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Author Contribution

The contributors of this study include MunaYehia and Fatima J. Al_Gawhari who both agree to the publication of this study.

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النهج الصيدلاني لجزيئات النانو كنظام توصيل يستهدف الدماغ

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الخلاصة

كانت اول دراسة تم الابلاغ عنها لتوصيل ادوية الدماغ الانفية ١٩٣٧. تلقى امتصاص توصيل الادوية في الدماغ-الانف قدرا كبيرا من الاهتمام كطريقة مريحة للادخال النظامي للادوية والتي تكون منخفضة واقل فعالية عن طريق الفم, وفعالة فقط اذا تم اعطاؤها عن طريق الحقن. يتأثر الاضمحلال الحيوي للادوية التي يتم ادخالها في تجويف الانف بشكل رئيسي بالخصائص الصيدلانية والحركية الدوائية للادوية وقد تم التحقق من كل ناقلات النانو تقريبا حتى الان لتوصيل الادوية من الانف الى الدماغ بما في ذلم المستحلبات النانوية والجسيمات النانوية الصلبة والمعلقات النانوية. ومع ذلك هناك العديد من التحديات المحتملة المرتبطة باعطاء الناقلات النانوية عن طريق الانف مثل السمية والتهيج في الغشاء المخاطي للانف واحتمالية الاضمحلال الانزيمي خلال الدخول. بشكل عام يمكن تحسين الالتصاق باضافة بوليمرات صناعية مثل حامض لمشتقات الايودراجيتللاكرليك والميثاكريليك.ان مصير الحاملات النانوية يعتمد على صفاتها الفيزيائية الكيميائية مثل مكونات حجم الجزيئات وشحنة سطح الجسيمات وكذلك كونه كاره ومحب للماء. تم استخدام نماذج تجريبية مختلفة في الدراسات المنشورة في المختبر او في الجسم الحي الى جانب زراعة الخلايا ونماذج خط الخلايا. ان التحليل الكمي كنسبة الدواء في الدم الى الدماغ اضافة الى التوافر الحيوي المطلق والنسبي للدواء والمستلم من الدماغ علاوة على ذلك, ان التحليلالنوعي يجب ان يشخص لمعظم الجسيمات النانوية ومظهرها الخارجي مثل التصوير البصري وعلم امراض الانسجة في الدماغ والمجهرالمضيء و ومضات كاما. في مقالة المراجعة القادمة, قُدم استعراضا مفصلا لادبيات المراجعة متعلقة بنظام استلام الدواء من الانف الى الدماغ بشكل مباشر

الكلمات المفتاحية: نظام توصيل، داخل الانف، حركية الدواء،جسيمات نانوية، تهديف من الانف الى الدماغ.